Mechanisms in Cytokine Signaling

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Hematopoiesis is regulated through the interaction of a variety of cytokines with their cognate receptors. The majority of cytokines, including erythropoietin (Epo), thrombopoietin (Tpo), granulocyte colony stimulating factor (G-CSF) and Interleukin-3 (IL-3) bind to receptors of the cytokine receptor superfamily. This receptor family shares structural motifs in the extracellular domain. In the cytoplasmic domains the receptors lack known motifs but share limited similarity in the membrane proximal region. This region binds one or more Janus protein tyrosine kinases (Jaks). The Jaks are 120-140 kDa cytoplasmic kinases which contain a carboxyl kinase catalytic domain and, immediately amino terminal, a pseudokinase domain. The amino terminal region contains no known protein motifs but contains regions of similarity among the Jaks. The receptors for Epo, IL-3 and Tpo specifically bind Jak2; the G-CSF receptor binds Jak1 and Jak2; and in the case of the IL-2 receptor, the β chain binds Jak1 while the γ_c chain binds Jak3. Following ligand binding, receptor dimerization/oligomerization brings the Jaks into sufficient proximity for trans "autophosphorylation" and activation of kinase activity. The activated Jaks are multiply phosphorylated and phosphorylate one or more of the receptor chains. Receptor and Jak phosphorylations result in the creation of "docking" sites for proteins that contain SH2 domains which bind to phosphotyrosine within specific sequence contexts. Through this mechanism the majority of cytokine receptors recruit SHC to the receptor complex which results in its phosphorylation and the activation of the sequence of events associated with the ras pathway. Other signaling proteins that are similarly recruited and activated include Vav, the p85 subunit of PI 3-kinase and 4PS/IRS-1. In addition, members of signal transducers and activators of transcription (Stat) family of transcription factors are recruited and activated. The Stat proteins vary in size from 85-115 kDa and are characterized by a carboxyl SH2 domain and an SH3 domain that is immediately amino terminal. The Stats utilize a novel DNA binding domain and contain no other known protein motifs. Phosphorylation at a single, carboxyl site results in dimerization, nuclear translocation and acquisition of DNA binding activity. Lastly, the phosphorylated receptor complex contains binding sites for a protein tyrosine phosphatase termed HCP. Recruitment of HCP to the receptor complex negatively influences the complex by de-phosphorylating and inactivating the Jaks. The relative roles of individual biochemical events in the biological responses has been assessed with receptor mutants that have lost the ability to mediate one or more of the biochemical responses. Together the data provide a generalized model for the mechanisms by which cytokine receptor initiate the events controlling growth and differentiation of hematopoietic cells